NUFFIELD COUNCIL ON BIOETHICS

BACKGROUND PAPER

The regulatory and legal situation of human embryo, gamete and germ line gene editing research and clinical applications in the People's Republic of China

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Note
The authors were commissioned by the Nuffield Council on Bioethics to write this paper in order to inform the Council's discussions about possible future work on this topic. The paper is intended to provide an overview of key clinical, ethical, social, legal and policy issues, but is not intended to offer any conclusions or recommendations regarding future policy and practice. Any views expressed in the paper are the views of the authors and not those of the Nuffield Council on Bioethics.

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Summary

1 This paper provides an overview of the regulatory and legal landscape for human gamete, embryo and germ line genome editing in the People's Republic of China. The paper reviews the situation for basic, preclinical and clinical research and potential commercial applications. Relevant policies and provisions are discussed in relation to some of the historical, socio-economic, political and cultural factors that shape bio-medical innovation in China, and that influence issues such as implementation, enforcement, levels of compliance, as well as public opinions and debates on human germ line research.

Introduction

2 The arrival of CRISPR-Cas9 technology offers new possibilities to introduce heritable genetic changes in human gametes, embryos and the human germ line. China in particular has played a role in pushing this field ahead. The first studies that reported genetic modification of human zygotes and embryos were published by researchers in China; and the Chinese government and companies have set aside funds to support this field of research. At the same time, little is presently known about the regulatory, legal, but also cultural, scientific and political conditions under which this research is conducted and most likely will be used in humans in the future.

3 In this background paper we begin to address this gap. Based on an analysis of existing English and Chinese-language literature, legal and regulatory provisions and other publicly available resources, we provide a broad overview of China's current regulatory environment for human genome editing. These insights are relevant not only because there is a widespread interest in Sino-British and Sino-European research collaborations, but also because technology developments in China do not stop at its borders, but have an impact on people and researchers in other countries. A comparative understanding of regulatory realities in this technology field may help in this regard to identify common ground, shared concerns but also differences that need to be understood and addressed.

Section 1: Governance structures for biomedical innovation in China

4 Since the start of China's transition from a centrally planned to a market-oriented economy in 1978, science and technology (S&T) research and applications have

become a key strategy for the country's economic and social development. The rapid growth of the Chinese S&T sector is exemplified by the fact that China surpassed Japan as the second largest investor of R&D expenditures in 2006 and that the country has awarded more science and engineering bachelor's degrees since 2012 than the USA and European Union combined.[1] Innovation in health biotechnology has become a priority especially since the 1990s, when a boost in funding under the *Ninth Five Year Plan (1996-2001)* led to the development of new infrastructures, institutions and research capacity.[2] China's research base in the life and health sciences has rapidly advanced since then and simultaneously experienced an ongoing process of internationalization.[3] In the *Thirteenth Five Year Plan (2016-2020)*, China's health biotech industry was defined as a 'strategic emerging industry', with genomics research, personalized medicine treatments and regenerative medical techniques as key research areas 'to cultivate strengths for future development'.[4] CRISPR-based genome editing research intersects with all of these fields and was mentioned in the Five Year Plan as one of the 'strategic forward-looking major scientific issues' whose deployment should be strengthened to 'promote the development of transformative technologies for the future of China's industrial transformation'.[5]

1.1. Government bodies involved in the governance of biomedical innovation

5 Government institutions involved in the governance of biomedical innovation in China fall into two central categories: those set up to advance and govern science and technology; and those established to promote and regulate medical research and applications. Science and technology activities are governed by the Ministry of Science and Technology (MOST). Activities related to health care, medical research and family planning are managed by the National Health and Family Planning Commission (NHFPC, the former Ministry of Health) and the China Food and Drug Administration (CFDA).

1.1.1. Ministry of Science and Technology (MOST)

6 The Ministry of Science and Technology (MOST) plays a central role in the shaping and implementation of S&T policy as well as research funding. The MOST, together with the National Science Foundation of China (NSFC) allocate the majority of research funding in China.[6] In the NSFC, the Department of Health Sciences and the Department of Life Sciences are the two main funding agencies for health biotech research.[7]

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[1] National Science Foundation (NSF). (2012). Science and engineering indicators 2012. URL: http://www.nsf.gov/statistics/seind12/pdf/seind12.pdf

[2] Li, Z.Z., Zhang, J.C., Wen, K., Thorsteinsdóttir, H., Quach, U., Singer, P. A., and Daar, A. S. (2004). Health biotechnology in China—reawakening of a giant. *Nature Biotechnology*, *22*, DC13-DC18.

[3] Bound, K., Saunders, T., Wilsdon, J. and Adams, J., (2013). China's absorptive state: Research, innovation and the prospects for China-UK collaboration. Nesta. Available at: http://www.nesta.org.uk/sites/default/files/chinas_absorptive_state_0.pdf

[4] National Development and Reform Commission (2016). China's 13th Five Year Plan. Available at: http://en.ndrc.gov.cn/newsrelease/201612/P020161207645765233498.pdf

[5] http://www.gov.cn/zhengce/content/2016-08/08/content_5098072.htm

[6] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303
and website of the MOST

[7] http://health.nsfc.gov.cn

1.1.2. The National Health and Family Planning Commission (NHFPC)

7 The NHFPC (the former Ministry of Health) is in charge of drafting laws, regulations, policies and plans related to public health, including the ethical governance of biomedical research and applications. It oversees medical practice in state hospitals, medical institutions and is also responsible for population control and family planning.[8]

1.1.3. The China Food and Drug Administration (CFDA)

8 The CFDA is an independent ministerial-level agency in China, responsible for the supervision of the safety management of medicines, food and cosmetics products. The authority is in charge of the licensing and administration of new medicines and medical devices, which includes supervising clinical trials and other forms of medical research.[9]

1.1.4. Other Government bodies involved in biomedical innovation

The China National Centre for Biotechnology Development (CNCBD)

9 The CNCBD is a subunit of the MOST and responsible for governing biotechnology including medical technologies. It is in charge of the management of China's biotech programs and the development and enforcement of biotechnology policies.[10]

The Chinese Academy of the Science (CAS)

10 The CAS is the national academy for the natural sciences in China and includes a network of altogether 104 research institutions, some of which are involved in bioscience and biotechnology research. The Shanghai Institute for Biological Sciences of CAS is widely recognized as the leading biological research institute in China.[11] The CAS functions as an infrastructure for high-level research, science education and serves as an academic governing body.[12]

The Chinese Academy of the Medical Sciences (CAMS)

11 The CAMS plays a leading role in modern medicine research in China. Founded in 1956, it is the only national-level academic center for the medical sciences in China.

12 It operates under the control of the NHFPC and is responsible for advising the government on pivotal health care and medical education reforms. It also comprises an infrastructure of 19 research institutes, 6 hospitals, 7 medical schools and 35 ministerial key laboratories scattered all over China.[13]

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[8] http://en.nhfpc.gov.cn
[9] http://eng.sfda.gov.cn/WS03/CL0755/
[10] http://www.cncbd.org.cn/
[11] http://english.sibs.cas.cn/au/bi/
[12] http://english.cas.cn
[13] http://english.cams.cn/index.html

The National Natural Science Foundation (NSFC)

13 The NSFC is under direct control of the State Council and manages the National Natural Science Fund, to promote and finance basic and applied research in China.[14]

1.2. Regional Governance of Biomedical Innovation

14 Even though China has a centralized political system, the provincial governments and the four municipal governments of Beijing, Tianjin, Shanghai and Chongqing (which have provincial-level status) have considerable autonomies. National level regulations for health biotech research often serve only as general guidance, which are then interpreted and defined at a provincial level, flexibly.[15] This can result in significant variation in the implementation of regulatory standards. Both, the NHFPC and the CFDA have branches at a provincial level. Although these institutions are accountable to their national counterparts, local interests and links with regional officials, scientists and companies can result in lenient enforcement of regulatory rules. As Warrell and colleagues conclude in a Medical Research Council (MRC) report on China-UK bioscience collaborations, these local alliances and the vast territory of China make it 'sometimes difficult for the national ministries to get accurate data about what is happening in remote regions, let alone to govern them'.[16] This situation is still occurring today and is also likely to affect the governance of human genome editing research, including the governance of clinical trials and potential clinical applications.

1.3. Military Governance of Biomedical Innovation

15 Another characteristic of China's governance system for biomedical innovation is that military medical institutions (which include hospitals and medical universities) are governed by the Health Department of the Army General Logistics Department (AGLD) - not by the NHFPC. Typically, regulatory documents from the NHFPC are merely a reference for governance, with the Military Health Department devising its own regulatory rules and supervision practices.[17] Therefore, military hospitals and research departments in military universities fall outside the authority of the NHFPC. This can result in an increased level of experimental freedom. It can also lead to clinical research and applications that would not be permitted in state institutions. In other research areas, such as stem cell medicine, this situation has attracted cooperation with corporations and (civilian) researchers (from both within and outside China), who have benefitted from the more permissive regulatory environment in military

[14] http://www.nsfc.gov.cn/publish/portal1/
[15] Zhang, J. Y. (2012). *The cosmopolitanization of science: stem cell governance in China*. Palgrave Macmillan.
[16] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303
[17] Sui, S., & Sleeboom-Faulkner, M. (2015). Governance of stem cell research and its clinical translation in China: An example of profit-oriented bionetworking. *East Asian Science, Technology and Society*, *9*(4), 397-412.

institutions.[18] It is possible that a similar development will also occur in the realms of human genome research.

1.4. Funding for biomedical innovation, including for human genome editing

16 The Chinese central government has played a significant role in the promotion and funding of the bioscience sector. The MOST funds basic research through the 973 Programme and the Centre for National Biotechnology Development (CNCBD) administers the biotech portion of the 863 Programme, which are the two largest S&T funding programmes in China.[19] Additional funds for biomedical innovation are provided by the National Natural Science Foundation (NSFC), the Chinese Academy of the Sciences and the funding programmes of the NHFPC. These provide money for preclinical and clinical research.[20] Additional funding is available from provincial and municipal governments.[21] The last two decades have also witnessed the increasing involvement of private sector companies. While the exact amount of funding from biotech and pharmaceutical companies is not known, private funding has significantly strengthened the development of China's health biotech sector.[22]

17 CRISPR-based gene editing research has until now primarily been funded through the NSFC and the 973 Programme. By October 2015, the NSFC had funded 57 projects involving CRISPR,[23] including the first two studies that reported human genome editing in human embryos.[24] Also the private sector is investing heavily in human genome editing research. While most of these funds flow into somatic genome editing research, corporate money has also been injected for human embryo genome editing research. Professor Junjiu Huang, the principal investigator of the first published human embryo gene-editing article,[25] has reportedly received three million Yuan of research funds from a private company called JinJia Group.[26]

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[18] Sui, S., & Sleeboom-Faulkner, M. (2015). (Same reference as previous footnote); Rosemann, A. (2014). Standardization as situation-specific achievement: Regulatory diversity and the production of value in intercontinental collaborations in stem cell medicine. *Social Science & Medicine*, *122*, 72-80.

[19] http://www.cncbd.org.cn/

[20] http://www.moh.gov.cn/qjjys/zdzx/list.shtml

[21] Salter, B. (2008). Governing stem cell science in China and India: emerging economies and the global politics of innovation. *New Genetics and Society*, *27*(2), 145-159; Bound, K., Saunders, T., Wilsdon, J. and Adams, J., (2013). China's absorptive state: Research, innovation and the prospects for China-UK collaboration. Nesta. Available at: http://www.nesta.org.uk/sites/default/files/chinas_absorptive_state_0.pdf

[22] Li, Z.Z., Zhang, J.C., Wen, K., Thorsteinsdóttir, H., Quach, U., Singer, P. A., and Daar, A. S. (2004). Health biotechnology in China—reawakening of a giant. *Nature Biotechnology*, *22*, DC13-DC18.;
Bound, K., Saunders, T., Wilsdon, J. and Adams, J., (2013). China's absorptive state: Research, innovation and the prospects for China-UK collaboration. Nesta. Available at: http://www.nesta.org.uk/sites/default/files/chinas_absorptive_state_0.pdf

[23] (Biological Discovery Network 2015)

[24] Liang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., ... & Sun, Y. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein & cell*, *6*(5), 363-372.;
Kang, X., He, W., Huang, Y., Yu, Q., Chen, Y., Gao, X., ... & Fan, Y. (2016). Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. *Journal of assisted reproduction and genetics*, *33*(5), 581-588.

[25] Liang, P., Xu, Y., Zhang, X., Ding, C., Huang, R., Zhang, Z., ... & Sun, Y. (2015). (Same reference as in previous footnote).

[26] Yang, N. (2015), JinJia and Zhongshan University signed a technology development cooperation contract. (In Chinese). Available at: http://www.cs.com.cn/ssgs/gsxw/201512/t20151230_4874293.html (accessed online January 21 2017).

Section 2: Review of current legal and regulatory frameworks for basic, preclinical and clinical research that involves human genome editing

18 Parallel to the building of research capacity the Chinese government has also been active on the regulatory and legal front. Since the 1990s state authorities have issued a wide range of regulatory instruments and laws to govern the burgeoning biomedical and bioscience sector in China. In this section we will provide an overview of relevant statutes, regulatory guidelines, ethical principles and administrative measures that apply to the genetic modification of gametes, embryos and the human germ line for both basic and preclinical research as well as clinical research and potential clinical applications. As we will show, only one regulatory instrument - the 2003 'Technical Norms on Human Assisted Reproductive Technologies' (人类辅助生殖技术规范) - addresses human gamete, embryo and germ line genome research directly. Article 3.9 of Part II of this document states that: 'The use of genetically manipulated human gametes, zygotes and embryos for the purpose of reproduction is prohibited'.[27] This clause in China's ART regulation does at present effectively ban clinical applications of genome editing in the context of human reproduction.

19 Another regulation that also addresses the use of genetically modified human cells are the two regulatory documents (1) 'Points to Consider in Human Somatic Cell Therapy and Gene Therapy Clinical Research' (人的体细胞治疗及基因治疗临床研究质控要点), which was issued by the MOH in 1993,[28] and (2) the 'Guiding Principles on Human Gene Therapy Research and Product Quality Control' (人基因治疗研究和制剂质量控制技术指导原则) that were promulgated by the MOH in 2003.[29] However, these two regulatory instruments apply currently exclusively to somatic forms of gene therapy and genome editing. Part I A of the 1993 document provides the following definition of gene therapy: 'A medical intervention based on modification of genetic materials of living cells'.[30] Of interest is that neither the 1993 nor the 2003 document on gene therapy specify the range of living cells that could be used for gene therapy. In other words, genetically modified cells derived from human embryos (such as genetically altered human embryonic stem cells [hESC]) as well as human gametes (such as genetically modified parthenogenetic stem cells or pluripotent stem cells derived from somatic cell nuclear transfer) can in principle be used for combined gene transfer / cell transplantation therapies. However, as mentioned above, the reproductive use of genetically altered gametes and embryos is effectively precluded by Article 3.9 of China's 'Technical Norms on Human Assisted Reproductive Technologies'.

2.1. Regulatory instruments in the Chinese legal system

[27] http://www.moh.gov.cn/mohbgt/pw10303/200804/18593.shtml
[28] http://www.whbiobank.com/news2/3000.jhtml
[29] http://www.sfda.gov.cn/WS01/CL0237/15708.html
[30] http://www.whbiobank.com/news2/3000.jhtml

20 The Chinese legal system consists of a variety of different regulatory categories and instruments. ***Laws*** (fa) are issued by the National People's Congress and are fully enforceable by the government bodies specified in a law. ***Regulations*** (tiaoli) are typically developed by (joint-)ministerial committees and are approved by the State Council. They are also enforceable.[31] ***Ministerial guidelines*** play the most important role in the governance of China's life and health science sector. While Chinese laws such as the 'Law on Practicing Doctors' (1999) and regulations such as the 'Regulation on the Administration of Medical Institutions' (1994) (both to be discussed in Section 2.4) set out high level guidance and statements of principles, ministerial guidelines manage institutional and research practices at a more detailed level.[32] Ministerial guidelines can either take the form of ***ethical guidelines*** (lunli zhidao yuanze) or ***ethical principles*** (lunli yuanze) or ***administrative measures*** (guanli banfa; in the literature sometimes also translated as 'regulatory rules'). ***Administrative Measures*** (guanli banfa) define the management and administration of specific forms of research or institutional practices. As defined in Articles 71 and 82 in the Legislation Law of the People's Republic of China (Gongheguo Lifafa) that was promulgated in 2000,[33] administrative measures are rules issued by ministries or other government bodies directly under the State Council. They are a source of legal norms in the Chinese legislation and are authoritative within the scope of the ministry or government body that has released them.[34] Administrative measures that address scientific or medical research and practice are binding for research institutions and hospitals, which are licensed by the NHFPC or the MOST to carry out these practices.[35]

21 ***Ethical guidelines*** (lunli zhidao yuanze) and ***Ethical Principles*** (lunli yuanze), on the other hand, shall guide new forms of research or technology in ways that are acceptable to public morality and that create social order. They are typically developed at a ministerial level and are enforceable only if they are specifically mentioned in a law, regulation or a ministerial administrative measure.[36] Another regulatory instrument are ***Technical Norms*** (jishu guifan) or ***Technical Standards*** (jishu biaozhun), which aim to ensure the safety and effectiveness of specific technologies. Like ethical guidelines they are enforceable only if authorized in regulations, laws or ministerial administrative measures.

22 It is important to note that in China many regulations or ethical guidelines start out as a ***'trial'*** (shixing) regulation (in the literature also sometimes translated as ***'interim'*** or ***'draft'*** regulation). A 'trial' regulation can be regarded as a valid,

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[31] Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf

[32] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303

[33] Legislation Law of the People's Republic of China. Available in English at: http://www.gov.cn/english/laws/2005-08/20/content_29724.htm

[34] Huo, Z.X. (2013) The People's Republic of China', In: Trimmings, K. and Beaumont, P. (eds.). 2013. *International surrogacy arrangements: legal regulation at the international level*. Bloomsbury Publishing.

[35] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303

[36] Huo, Z.X. (2013). (Same reference as in footnote 34).

formal regulation that is enforceable, but it is also flexible enough to leave space for change.[37]

2.2. Legal and Regulatory situation for Basic and Preclinical Research that involves Human Genome Editing

23 Basic and preclinical research that involves human gamete or embryo genome editing is regulated through a number of horizontal regulations. A regulation that specifically addresses basic/preclinical human genome editing is not yet in place. The regulatory landscape for basic and preclinical research in this field is permissive.[38] The following legal and regulatory instruments influence the decisions and possibilities of researchers who plan to genetically modify human gametes and embryos, and shape the procedures, mechanisms and methods through which this research is conducted.

2.2.1 China's Regulatory Framework for Artificial Reproductive Technologies (ARTs)

24 The Chinese regulation of ARTs provides the central regulatory framework for both basic and preclinical research as well as reproductive applications that involve human gamete or embryo genome editing. While the framework presently bans reproductive applications (as we will discuss in Section 2.3 below) it enables basic and preclinical research that involves genome editing.

25 A first regulatory rule for the governance of ARTs was issued by the MOH in 2001. The 'Administrative Measures for Assisted Human Reproductive Technologies' (MOH 2001)[39] officially authorized the use of ARTs at a national level, but imposed a ban on all forms of trade on human gametes, as well as fertilized eggs and IVF embryos. It also prohibited any form of surrogacy procedures.[40] It stated, moreover, that the use of ART shall strictly conform to China's family planning policy, and its corresponding laws and ethical standards.[41] In 2003 the MOH issued a revised ART regulation that included three parts:[42]

- The 'Ethics Guiding Principles of Assisted Reproductive Technologies and Human Sperm Banks' (人类辅助生殖技术和人类精子库伦理原则)
- The 'Technical Norms on Human Assisted Reproductive Technologies' (人类辅助生殖技术规范)
- The 'Basic standards and technical specifications for human sperm banks' (人类精子库基本标准和技术规范)

[37] Rosemann, A., & Sleeboom-Faulkner, M. (2016). New regulation for clinical stem cell research in China: expected impact and challenges for implementation
[38] Ishii, T. (2015). Germ line genome editing in clinics: the approaches, objectives and global society. *Briefings in functional genomics*, elv053.
[39] http://www.moh.gov.cn/mohbgt/pw10303/200804/18593.shtml
[40] http://www.nhfpc.gov.cn/mohzcfgs/s6729/200804/29342.shtml
[41] Huo, Z.X. (2013) The People's Republic of China', In: Trimmings, K. and Beaumont, P. (eds.). 2013. *International surrogacy arrangements: legal regulation at the international level*. Bloomsbury Publishing.
[42] http://www.moh.gov.cn/mohbgt/pw10303/200804/18593.shtml

26 The 'Ethics Guiding Principles of ART and Sperm Banks' set out some basic ethical principles under which ARTs should be applied in Chinese society. ***These are also relevant for research that involves the genetic modification of gametes, zygotes and embryos*.** These principles include, respect for patient autonomy and privacy, the protection and safeguarding of the interests of offspring, the prevention of commercialization and a commitment to common good.[43]

27 The 'Technical Norms on Human Assisted Reproductive Technologies', on the other hand, stipulate the conditions under which ARTs should be applied in medical institutions. Article 3.9 of Part II of these Technical Norms states that: 'The use of genetically manipulated human gametes, zygotes and embryos for the purpose of reproduction is prohibited'.[44]

28 Nevertheless, while this document bans the genetic manipulation of human gametes, zygotes and embryos for reproductive purposes (Section 2.3 below), it allows the use of genetically modified reproductive tissues for basic and preclinical research. Most importantly, it plays the key role in regulating the donation and transfer of human embryos and gametes for basics and preclinical research use. Together with the 'Basic Standards and Technical Specifications of Human Sperm Banks' (which regulate the donation and reproductive and research use of sperm) the 'Technical Norms on Human Assisted Reproductive Technologies' shape basic and preclinical research that involves the genetic modification of gametes or embryos in the following five ways:

- By stipulating that ART institutions must set up ethics committees, and that these committees must review and approve the donation and use of human embryos for research
- By restricting the use of embryos for research to super-numerous embryos derived from IVF, and by prohibiting the creation of IVF embryos for research only.
- By clarifying that embryos and gametes must be voluntarily donated, on the basis of informed consent.
- By forbidding hormonal super-stimulation, to harvest a larger number of oocytes. This regulation is backed up by punitive measures: IVF clinics or ART centers can loose their license if they violate these guidelines.[45]
- By stipulating that the buying and selling of human ova, sperm, embryos or fetal tissues is prohibited. This does also include the selling of genetically modified gametes and embryos, including the prohibition to patent genetically modified gametes and embryos (see below: 'Guidance for Patent Examination').

29 National oversight of these ministerial guidelines occurs through a licensing system for IVF clinics.[46] A license can be withdrawn by the NHCFP (the former

[43] MOH 2003
[44] http://www.moh.gov.cn/mohbgt/pw10303/200804/18593.shtml
[45] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303
[46] Warrell, D. et al. (2009). (Same reference as in previous footnote).

MOH), which will result in the closure of ART centers,[47] which has happened in the past.[48]

2.2.2 The Ethics Guiding Principles for hESC research (Ministry of Health and Ministry of Science and Technology; 2003)

30 The derivation of human embryonic stem cells (hESC) and the use of these cells for research is regulated with the 'Ethics Guiding Principles for hESC research' (2003) (人胚胎干细胞研究伦理指导原则). These are ministerial guidelines joint-issued by the MOH and the MOST in 2003.[49] *This regulation is of relevance to basic and preclinical research that involves the genetic modification of gametes and embryos for various reasons*:

- It sets out that embryos are not allowed to be used for the derivation of hESC after 14 days post-conception.
- Embryos that are used for research cannot be implanted in human beings.
- The document demands, furthermore, that institutions that conduct research with human embryos and their derivates must form an ethics committee, which is required to detail the exact rules and conditions under which research can be conducted.

31 Another important aspect of these joint-ministerial guidelines is that although they prohibit human reproductive cloning, they allow for the creation of research embryos from parthenogenesis and somatic cell nuclear transfer ('therapeutic cloning').[50]

32 Of interest is also, that these guidelines do not specifically address (or prohibit) the possibility to create human germ cells from pluripotent hES cells, or alternatively from induced pluripotent stem (iPS) cells. Embryos created from these in-vitro-created (or "artificial") germ cells, as has widely been reported, could form a vital resource for human genome editing research.[51] However, even though the creation of in-vitro-created (or "artificial") germ cells is possible, in-vitro-created germ cells could not be used for the creation of hESC lines. Article 5 of the 2003 Ethics Guiding Principles for hESC research stipulates: 'hESC for research can only be derived from the following:

1. surplus gametes or blastocysts from IVF

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[47] Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf

[48] Qiao, J., & Feng, H. L. (2014). Assisted reproductive technology in China: compliance and non-compliance. *Translational pediatrics*, *3*(2), 91.

[49] http://www.most.gov.cn/fggw/zfwj/zfwj2003/200512/t20051214_54948.htm

[50] Ishii, T. (2015). Germline genome-editing research and its socioethical implications. *Trends in molecular medicine*, *21*(8), 473-481.;
Döring, O. (2003). China's struggle for practical regulations in medical ethics. *Nature Reviews Genetics*, *4*(3), 233-239.; McMAHON, D. S., Thorsteinsdóttir, H., Singer, P. A., & Daar, A. S. (2010). Cultivating regenerative medicine innovation in China. *Regenerative Medicine*, *5*(1), 35-44.

[51] Ishii, T. (2015). Germ line genome editing in clinics: the approaches, objectives and global society. *Briefings in functional genomics*, elv053.;
National Academies of Science (2017). Human Genome Editing: Science, Ethics and Governance. Available at: https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance

2. cells from human fetuses left by natural abortion or voluntary abortion
3. blastocysts or parthenogenetic blastocysts obtained by somatic cell nuclear transfer technology
4. reproductive cells from voluntary donation'

Criticism of the Ethics Guiding Principles for hESC research

33 The ethical guidelines for hESC research have been criticized for various reasons. Xiaomei Zhai, for example, a member of the National Ethics Committee of the NHFPC, has stated that the system of oversight for basic or preclinical forms of hESC research is underdeveloped. There is no registration or licensing system of research institutes that conduct basic or preclinical hESC research.[52] (However, there is now a licensing system in place for clinics and researcher that conduct clinical stem cell research. This will be explained in Section 3.4. below). Moreover, punitive measures for (basic and preclinical) hESC researchers who transgress the ethical principles laid down in the guidelines are insufficiently defined, because they are not backed up by law.[53] In addition, as pointed out by Warrell and colleagues, 'the guidelines include no provision for national supervision to ensure their implementation. They merely require research institutions to formulate "detailed measures and regulatory rules" and to establish an ethical committee to supervise hESC research'.[54] While plans to revise these guidelines have been reported already in 2007,[55] an updated version of these guiding principles has not yet been published.

34 The critique that the registration or licensing system of research institutes who engage in hESC is underdeveloped ***is also likely to apply to embryo or germ cell research that involves genome editing***. In contrast to the UK, where all forms of embryo research have to be approved and licensed by the Human Fertilization and Embryology Authority (HFEA), in China no such national licensing system exists and ethical approval lies entirely in the hand of the ethics committees of local institutions.

2.2.3. The Administrative Measures for Human Genetic Resource Management (1998)

35 An additional regulatory instrument that applies to human genome editing are the 'Administrative Measures for Human Genetic Resource Management' (人类遗传资源管理暂行办法), which were joint-issued by the MOH (now the NHFPC) and the MOST in 1998.[56] These Measures specify rules and application procedures for the donation, research and institutional transfer of human genetic materials. The term "human genetic materials" as used in these Measures refers to

[52] Zhai, X.M. (2007). Challenges and Governance - Regulatory Responses in China. Conference paper, BIONET workshop: October 2007, Shanghai.
[53] Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf
[54] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303
[55] Zhai, X.M. (2007). Challenges and Governance - Regulatory Responses in China. Conference paper, BIONET workshop: October 2007, Shanghai.
[56] http://www.most.gov.cn/fggw/xzfg/200811/t20081106_64877.htm

'organs, tissues, cells, blood, preparations, recombinant deoxyribonucleic acid (DNA) constructs containing human genome, genes and related products'.[57] This definition clearly applies to genetically modified gametes, embryos and their derivates.

36 The 1998 Measures are enacted through the Chinese Human Genetic Resources Control Office (HGCO), which serves as the coordinating agency and handles approval and other administrative procedures.[58] They require informed consent from tissue donors and relatives, but do not provide information about the content and form of informed consent procedures. They also do not request IRB review, which was widely criticized.[59] To compensate for this shortcoming, the MOH promulgated the 'Administrative Measures for the Ethical Review of Biomedical Research involving Human Subjects' in 2007 (see next section), which requested IRB review for all forms of biomedical research that involve human subjects, including tissue donors.

37 Another key function of the 1998 Administrative Measures for Human Genetic Resource Management is to control the import and export of genetic resources from and to China and to prevent the financial exploitation and potential misuse of Chinese genetic resources by foreign and corporations, which is relevant especially in the context of international collaborations. One aspect that is important in this regard is the transfer of (reproductive) tissues outside of and into China.

Moving genetically modified gametes and embryos outside of and into China

38 In order to transport human tissues, cells, stem cells and potentially also *genetically modified human gametes, embryos or their derivates* to research institutes outside of China, the following requirements have to be met: *First,* to obtain approval from the 'Chinese Inspection and Quarantine Bureau, which handles an online registration system, and which has specified the conditions that apply to the transfer of human tissue in the 'Work Norms for the Health Quarantine Examination and Approval of the Entry/Exit of Special (Biological) Items', a nationally binding memorandum issued in 2006.[60] This document does not include distinct specifications for genetically modified human tissues and also not for human reproductive tissues, or their derivates such as hESC. These tissues 'fall under the same category as human blood, bone marrow, cord blood and other tissue commonly used for medical purposes'.[61] Documentation requirements for these tissue types 'include a range of standard operation procedures for the identification of cell identity, quality and the presence of microbial contaminants and biohazards. Further requirements include a description of research purposes and potential risks'. A second requirement is to set up a Material Transfer Agreement (MTA), a document that has to be signed

[57] MOH 1998
[58] Rosemann, A. (2011). Modalities of value, exchange, solidarity: the social life of stem cells in China. *New Genetics and Society*, *30*(2), 181-192.
[59] Wang, Z., Zhang, D., Ng, V. H., Lie, R., & Zhai, X. (2014). Following the giant's paces-governance issues and bioethical reflections in China. *BMC medical ethics*, *15*(1), 79.
[60] Rosemann, A. (2011). Modalities of value, exchange, solidarity: the social life of stem cells in China. *New Genetics and Society*, *30*(2), 181-192.
[61] Rosemann, A. (2011). (Same reference as in previous footnote).

by the Chinese Human Genetic Resources Control Office (HGCO). The MTA defines 'the conditions and terms of use of exchanged tissue as negotiated and agreed upon between the exchange partners. Besides issues related to intellectual property and benefit sharing, the document must include a technical description of the research, and a risk assessment and safety evaluation form. The HGCO checks also the license and qualifications of the tissue recipient abroad. Once the MTA has been authorized, a local branch of the Inspection and Quarantine Bureau issues a final approval document'.[62]

39 In case of the import of reproductive or embryonic tissues from a foreign country into China the same procedures apply. An application must be filed to receive approval from the Chinese Inspection and Quarantine Bureau, and the Chinese Human Genetic Resources Control Office reviews the conditions under which imported tissues shall be used.

Expected Changes for the Management of Human Genetic Resources in the Nearby Future

40 Some of these requirements are likely to change in the nearby future. As reported by Zhai, Ng and Lie,[63] the Chinese State Council has issued an initial draft of 'The Regulation of the Human Genetic Resources' (an updated and revised version of the Administrate Measures discussed in this section) for public comments. As the authors note:

'Although the regulation has not officially come into force yet, it would replace the former interim measures of 1998. The regulation officially requires IRB review for all genetic research and places further specific emphasis on genetic research. The draft requires that the collection and storage of human genetic samples should abide by principles of autonomy and informed consent. Before sample collection, written informed consent shall be offered to the donor to explain the purpose, usage, potential health risks, interest-sharing plans, privacy protection and other necessary relevant information about the research. Subjects have the right to quit unconditionally at any time. It also requires that re-consent should be requested if samples are used for other purposes beyond the initial consent'.[64]

41 The implications of these expected changes for human genome editing research, and more specifically, research that involves the genetic modification of human gametes, embryos (including embryos derived from in-vitro-created germ cells) and their derivates are at present not clear.

2.2.4 Guidelines for Patent Examination (2010)

42 Another ministerial guideline that affects basic and preclinical research that involves human genome editing is the 'Guidelines for Patent Examination' (专利

[62] Rosemann, A. (2011). (Same reference as in previous footnote).
[63] Zhai, X., Ng, V., & Lie, R. (2016). No ethical divide between China and the West in human embryo research. *Developing world bioethics*.
[64] Zhai, X., Ng, V., & Lie, R. (2016). No ethical divide between China and the West in human embryo research. *Developing world bioethics*.

审查指南) issued in 2010 by the State Intellectual Property Office (SIPO), which is the patent administration department of the State Council.[65]

43 A key characteristic of the Chinese Guidelines for Patent Examination is that it prohibits the patenting of human body parts and its derivatives. ***This prohibition also applies to genetically modified human gametes, embryos and derivative cells*.** As specified in Article 9.11.2 of Part II of the Guidelines, the 'human body, at the various stages of its information and development, including a germ cell, an oosperm, an embryo and an entire human body shall not be granted the patent right in accordance with the provisions of article 5.1 of patent law'. Article 5.1 of the Guidelines, which was promulgated by Order Nr. 55 of the State Intellectual Property Office,[66] is a moral exclusion clause that states that 'no patent right shall be granted for any invention–creation that is contrary to the laws of the State or social morality or that is detrimental to public interest".

44 According to the explanation by the Commission of Legislative Affairs,[67] the 'social morality' standard depends on its acceptability by the public. As specified in Article 3.1.2 of Part II of the Guidelines 'an invention-creation related to […] a process for modifying the germ line genetic identity of human beings or a human being thus modified […] is contrary to social morality' and therefore prohibited from being patented. The same is true for the patenting of human embryonic stem cells or other derivative cells that might be derived from genetically modified embryos. As stated in Article 9.1.1.1 in Part II of the Guidelines, 'both an embryonic stem cell of human beings and a preparation method thereof shall not be granted the patent right in accordance with the provisions of Article 5.

45 On the other hand, as laid down in Article 9.1.2.2 of Part II of the Guidelines, 'a gene or DNA fragment', that has been created by manipulating 'genes artificially by gene recombination, cell fusion, etcetera' can be patented, at least if it can be demonstrated to have medical or industrial benefits.[68] This can under specific circumstances also apply to modified human DNA fragments. While Article 25 of the Guidelines precludes 'methods of [genetic] diagnosis and treatment' from being patented, it allows patenting of the substances or materials used in disease treatment. For this reason, as the legal experts Wei Li and Li-Sheng Cai point out, a method of treating a disease that uses new genes can be strategically converted into the 'use of new genes [as a material] in preparation of drugs treating tumors [or other disorders]' and therefore 'become patentable subjects'.[69]

2.3. The legal and regulatory situation for clinical research and applications that involves heritable genome editing in humans

46 At present only clinical trials using somatic gene editing are legally permissible in

[65] http://www.sipo.gov.cn/zhfwpt/zlsqzn/sczn2010eng.pdf
[66] http://english.sipo.gov.cn
[67] Jiang, L. (2016). *Regulating Human Embryonic Stem Cell in China: A Comparative Study on Human Embryonic Stem Cell's Patentability and Morality in US and EU*. Springer.
[68] Li, W., & Cai, L. (2014). The scope of patent protection for gene technology in China. *Nature biotechnology*, *32*(10), 1001.
[69] Li, W., & Cai, L. (2014). (Same reference as in previous footnote).

China. Clinical research and applications that involves heritable changes of human reproductive tissues are banned as part of China's ART regulation.[70] As promulgated in Article 3.7 and 3.9 of the 'Technical Norms of Human Assisted Reproductive Technologies' in 2003 'gene manipulation on human gametes, zygotes and embryos for the purpose of reproduction is banned'.[71]

47 Based on a comparison of the regulatory landscape for human germ line gene modification in 39 countries, the legal scholar Tetsuya Ishii has introduced a distinction between "ban by legislation" and "ban by guidelines".[72] According to Ishii, China has banned 'germ line modification under guidelines, which are less enforceable than laws [i.e. ban by legislation] and are subject to amendment'.[73] While it is true, that the 2003 Technical Norms on Human Assisted Reproductive Technologies have the legal status of ministerial guidelines and not laws, this does not mean that the ban for reproductive uses of genetically modified reproductive tissues is without teeth.

48 The reason is that according to the 2003 Technical Norms on Human ARTs, IVF clinics and ART centers must be authorized and certified by the NHFPC. Once approved an ART centre receives a certificate from NHFPC and it must provide documentation and annual reports to the NHFPC.[74] If ART centers offer unauthorized or illegal services, the NHFPC has the legal authority to withdraw licenses of medical institutions that provide ART services on the basis of the 'Regulation on the Administration of Medical Institutions', issued by the State Council in 1993. License withdrawal results automatically in the shutting down of these institutions.[75]

49 Despite this, and even though the NHFPC has shut down a larger number of unapproved IVF clinics in the mid-2000s, 'a "grey zone" of an uncounted number of unauthorized private clinics' has re-surfaced in recent years 'as some individuals are prepared to risk punishment by providing ART services without a license, lured by an ever-growing demand for ART services and the potential of huge business profits'.[76] This problem has increased since 2016, when the transition from China's one-child to a two-child policy has resulted in a growing demand for IVF treatments.[77]

50 But there are also reports of other illegal services that are provided in Chinese

[70] Ishii, T. (2015). Germ line genome editing in clinics: the approaches, objectives and global society. *Briefings in functional genomics*, elv053;
Zhai, X., Ng, V., & Lie, R. (2016). No ethical divide between China and the West in human embryo research. *Developing world bioethics*.
[71] MOH 2003
[72] Ishii, T. (2015). Germ line genome editing in clinics: the approaches, objectives and global society. *Briefings in functional genomics*, elv053.
[73] Ishii, T. (2015). Germline genome-editing research and its socioethical implications. *Trends in molecular medicine*, *21*(8), 473-481.
[74] Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf
[75] Doering, O. and A. Wahlberg (2007). (Same reference as in previous footnote).
Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303
[76] Doering, O. and A. Wahlberg (2007). (Same reference as in footnote 74).
[77] Xie, Y.Q. and H. Xiao (2016). Analysis of Mental Health Related Factors of ART in Treatment of the Elderly Infertile Female with One Child. Reproduction & Contraception. 2016-12. (In Chinese).

ART centers, such as sex selection (which is prohibited by ART guidelines) and especially surrogate motherhood services. While surrogate motherhood has been prohibited in China since 2001, a large informal market for surrogacy services has emerged in recent years.[78] Surrogate mothers are hired as reproductive laborers and paid monthly wages, that fluctuate with the stages of pregnancy.[79] According to an article from the Chinese newspaper South China Morning Post, the Chinese government is now seeking to respond to this informal market by making surrogacy legal, which would allow a greater level of control and safeguards for both surrogate mothers and their clients.[80] This situation shows, that Ishii's concern above – that a ban for heritable genome editing 'by guidelines' is less enforceable than a 'ban by legislation' may partly be justified.

2.4 Existing horizontal regulations that would regulate heritable germ line applications, if China's ban on reproductive use was lifted

51 If safety concerns for human genome editing can be alleviated, a future amendment of the current ban for reproductive uses of heritable forms of genome editing in humans is not unthinkable. Should this happen, the following horizontal regulatory instruments would currently be in place to regulate – at least certain aspects – of clinical applications of heritable forms of genome editing. However, additional regulatory instruments that address the specific characteristics and risks of germ line genome editing in clinical applications – would be urgently required.

2.4.1. The Notification on Ethical Review of Biomedical Research Involving Human Subjects' (MOH; 2007) and the Measures for the Ethical Review of Biomedical Research Involving Humans (NHFPC, 2016)

52 The 'Notification on ethical review of biomedical research involving human subjects' (涉及人的生物医学研究伦理审查办法通知 [试行]) has been issued by the Ministry of Health in 2007.[81] This notice stipulates that all forms of research and experimental clinical interventions that involve human subjects require ethical review by an independent ethics committee at the level of a research institute or hospital. The regulation provides detailed information on the procedures and criteria for ethics committee review, the structure of the committees as well as details on informed consent procedures. This notice would be applicable to clinical applications that involve heritable genome editing, should such a step be taken in the future.

53 In 2016 the NHFPC further clarified the responsibilities and tasks of medical ethics committees, by issuing the 'Measures for the Ethical Review of Biomedical

[78] Yan, A. (2017). Official Ban is No Brake on China's Surrogacy Sector. South China Morning Post (February 17, 2017). Available at: http://www.scmp.com/news/china/society/article/2071548/official-ban-no-brake-chinas-surrogacy-sector
[79] Su, Y.Y. (2017). Public Opinion on Legalizing Surrogacy in China?. Impact Ethics. Available at: https://impactethics.ca/2017/03/15/public-opinion-on-legalizing-surrogacy-in-china/
[80] Yan, A. (2017). (Same reference as in footnote 78).
[81] http://www.moh.gov.cn/mohbgt/pw10702/200804/18816.shtml

Research Involving Humans' (涉及人的生物医学研究伦理审查办法).[82] These Measures substantiated the content of the 2007 Notification by providing additional details on the principles, processes, standards and supervision of ethical review processes. It also specified in greater detail the responsibilities and tasks of medical ethics committees; not only at medical institutions but also at the national and provincial level. Important is, as Xinqing Zhang and colleagues point out in a recent publication, that ethics committees of medical and health institutions are now required to 'implement measures for improvement put forward by health and family planning authorities at the county level or above'.[83]

54 The 2016 Measures, in short, introduce a much needed oversight system for institutional research ethics committees. It introduces a regional inspection system and when research ethics committee fails to comply or has violated existing norms, serious consequences can follow. As Zhang and co-authors mention, personnel is held legally accountable and the chair of a committee can be removed. Moreover, for 'high-risk research projects, a research ethics committee shall convene plenary sessions for review and increase the frequency at which researchers submit their research progress reports (for example once every three months or on a case by case basis).[84]

2.4.2. Regulation on the Governance of Medical Institutions (State Council; 1994)

55 The 'Regulations on the administration of medical institutions' (医疗机构管理条例实施细则) was issued by the State Council in 1994.[85] The regulation stipulates performance rules for medical institutions such as registration procedures, required qualifications of medical staff, as well as institutional safeguards that shall prevent the misuse of patients. It clarifies, for example, that informed consent is a mandatory requirement for the participation of patients in clinical studies, surgical operations and other experimental medical interventions. This regulation (as mentioned already in Section 2.3) is relevant for reproductive uses of genetically modified gametes, zygotes or embryos, because it summons that medical institutions (i.e. ART centers and IVF clinics) can loose their license and be shut down if they provide unauthorized or illegal treatments.

2.4.3. The Law on Practicing Doctors of the People's Republic of China (National People's Congress; 1999)

56 The 'Law on Practicing Doctors of the' (中华人民共和国执业医师法), issued by the National People's Congress in 1999, addresses the duties and responsibilities of

[82] http://www.nhfpc.gov.cn/fzs/s3576/201610/84b33b81d8e747eaaf048f68b174f829.shtml
[83] Zhang, X.Q., Zhang W.X., and Zhao, Y.D. (2016). The Chinese Ethical Review System and its Compliance Mechanism. Available at: http://trust-project.eu/wp-content/uploads/2016/03/Chinese-Ethics-Review-System.pdf
[84] Zhang, X.Q., Zhang W.X., and Zhao, Y.D. (2016) (Same reference as in previous footnote).
[85] http://www.moh.gov.cn/zwgk/wlwl/200804/df7aa8d42a2b4692ac7d7ff04bf7d173.shtml

practicing doctors in the context of clinical trials and research.[86] It states that doctors who violate patient's privacy, expose them to undue risks, or who conduct experimental medical interventions without informed consent will be legally prosecuted. This law protects patients by allowing them to sue their physicians, if they experienced malpractice or if their treatment was based on deceptive or fraudulent claims.[87]

2.4.4. The regulatory framework for gene therapy

57 China's regulatory framework for gene therapy would most likely play a role also for the regulation of heritable forms of genome editing, at least if China's current ban on reproductive gene editing would be lifted in the future. The MOH made a first attempt to regulatory gene therapies in 1993, when it published the document 'Points to Consider in Human Somatic Cell Therapy and Gene Therapy Clinical Research' (人的体细胞治疗及基因治疗临床研究质控要点).[88] This document emphasized especially the need for a reliable scientific review process for gene therapy trials, which was not the norm at this time. Ten years later, in 2003 the SFDA published the 'Guiding Principles on Human Gene Therapy Research and Product Quality Control' (人基因治疗研究和制剂质量控制技术指导原则), which were issued in 2003.[89] Also this document does not make any references to gene therapy that would involve human reproductive cells, and it does also not prohibit or refer to the provision of gene therapy in the context of human reproduction. The 2003 document stipulates procedures for quality control, manufacturing requirements, procedures to evaluate the safety and efficacy of a candidate treatment, review criteria for local IRBs. The guidelines also state that gene therapy trials have to adhere to the ethical requirements set out in the 'Drug Clinical Trial Quality Specifications' (药物临床试验质量管理规范), that were introduced by the CFDA in the same year.[90]

58 Part I A of the 1993 document provides the following definition of gene therapy: 'A medical intervention based on modification of genetic materials of living cells'.[91] However, neither the 1993 nor the 2003 regulation on gene therapy specifies the range of living cells that can be used for gene therapy. This means that genetically modified cells derived from human embryos (such as genetically altered human embryonic stem cells [hESC]) as well as human gametes (such as genetically modified parthenogenetic stem cells or pluripotent stem cells derived from somatic cell nuclear transfer) can in principle be used for combined gene transfer / cell transplantation therapies (as long as this is in the realms of somatic gene therapy).

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[86] English Version of the Law: http://www.cma.org.cn/ensite/index/HealthcareSystem/20101115/1289827560328_1.html; Chinese version: http://www.pkulaw.cn/fulltext_form.aspx?Db=chl&Gid=20221

[87] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303

[88] http://www.whbiobank.com/news2/3000.jhtml

[89] http://www.sfda.gov.cn/WS01/CL0237/15708.html

[90] http://www.sda.gov.cn/WS01/CL0053/24473.html

[91] Same reference as in previous footnote.

59 While the 2003 guidelines for gene therapy stipulated family consent as a mandatory requirement for participation in gene therapy trials, Zhang argued in 2005 that individual consent could be a better option, especially if there are disagreements between a patient and his family in the consent process.[92] In 2009, the MOH issued the 'Administrative Measures for the clinical use of biomedical technologies; (医疗技术临床应用管理办法), which classified gene therapy as a Class III – high risk – medical technology that can only be approved for clinical use after systematic clinical research, and after being licensed by the CFDA.[93]

60 While at present these two regulatory instruments play only a role for somatic forms of human genome editing, they could in the future possibly also play a role in the regulation of clinical applications that involve heritable forms of human genome editing (provided China's ban would be lifted).

2.4.5. The Drug Clinical Trial Quality Specifications (CFDA; 2003)

61 The 'Drug Clinical Trial Quality Specifications' **(**药物临床试验质量管理规范**)** are a set of technical standards that were issued by the CFDA in a first version in 1999 and in a second, updated version in 2003.[94] The 'Drug Clinical Trial Quality Specifications' specify procedures for clinical trials in the context of investigational new drugs or new biologics applications. They also stipulate procedures for the accreditation of medical institutions that take part in drug trials or other forms of medical experimentation authorized by the CFDA. The 'Drug Clinical Trial Quality Specifications' require mandatory informed consent for human research participants, assessment of the risks and benefits of a clinical study, and IRB approval in each hospital in which a (multi-sited) study is conducted. It also includes provisions on how IRBs should be composed and be organized. Enforcement of the 'Drug Clinical Trial Quality Specifications' is demanded by the National People's Congress's 'Drug Administration Law' (中华人民共和国药品管理法) that was issued in 2001 (and amended in 2015), which is joint-implemented by the National Health and Family Planning Commission. The law covers the use of pharmaceutical products (including biological products) in research as well as routine clinical applications following market approval.[95] [96]

62 *It is not clear to us, whether the 'Drug Clinical Trial Quality Specifications' and the 'Drug Administration Law' would play an active role in the regulatory oversight process for the clinical use of heritable genome editing in humans.* While a 2016 article by Zhai, Ng and Lie mentions the 'Drug Clinical Trial Quality Specifications' as a relevant regulation in a discussion of human germ line gene

[92] Zhang, X.Q. (2005). Gene Therapy in PR China: Regulations and Ethical Concerns. *Journal of International Biotechnology Law*, *2*(5), 212-216.
[93] http://www.nhfpc.gov.cn/zwgkzt/wsbysj/200903/39511.shtml
[94] http://www.sda.gov.cn/WS01/CL0053/24473.html
[95] The 2001 version of the Law in English: http://eng.sfda.gov.cn/WS03/CL0766/61638.html; and in Chinese: http://www.sda.gov.cn/WS01/CL0784/23396.html
[96] The 2015 amended version of the Drug Administration Law: http://www.sda.gov.cn/WS01/CL1030/124980.html

editing in China,[97] it is clear that the genetic modification of gametes, zygotes and embryos is fundamentally different from a drug-based approach of disease prevention. The applicability of these two regulatory instruments is questionable also because the clinical use of genetically modified gametes or embryos cannot be tested in a conventional clinical trial format. A first problem is that the possibility to work with a control group is precluded, since the testing of two different forms of genetic modification in gametes, zygotes or embryos to achieve the same result in an unborn human being would be highly unethical. All unborn human beings that would take part in a clinical study deserve the opportunity for the best possible life, and cannot be subjected to an increased risk of suffering disadvantages in order to determine whether one method works better than another. A second problem is that prospective parents have to provide consent to an experimental intervention and not the actual subject, who at the time of the experiment is not yet born (and in case a genetically modified sperm or egg is used has not even reached the earliest stage of human life).[98] A related problem is that, in the case of unintended genetic changes or unanticipated adverse effects not only the experimental subject him or herself is affected, but potentially also subsequent generations. A forth problem is that at present it is not yet entirely clear how potential benefits should be weighed against risks. Answers to this question will change as the technology advances and possible risks can be minimized. For these reasons, the 'Clinical Trial Quality Specifications' and also the 'Drug Administration Law' would have to be fundamentally revised to fit the needs of clinical studies that involve heritable forms of genome editing. A separate regulation that specifically addresses these needs would be required.

2.4.6. The Tort Liability Law of the PRC (National People's Congress, 2010)

63 The Tort Liability Law (中华人民共和国侵权责任法) of the People's Republic of China that was issued by the National People's Congress in 2010.[99] The Tort Liability Law plays a key role in protecting the legally defined rights and interests of civil subjects in China. They ensure in particular, 'citizens' right to life, to health as well as the right of privacy'.[100] Article 54, in chapter VII of the Tort Liability Law addresses 'Medical Malpractice' and specifies that 'where a patient sustains any harm during diagnosis and treatment, if the medical institution or any of its medical staff is at fault, the medical institution shall assume the compensatory liability'.[101]

[97] Zhai, X., Ng, V., & Lie, R. (2016). No ethical divide between China and the West in human embryo research. *Developing world bioethics*.
[98] Ishii, T. (2015). Germ line genome editing in clinics: the approaches, objectives and global society. *Briefings in functional genomics*, elv053.
[99] NPC (2010). The Tort Liability Law of the People's Republic of China. http://www.gov.cn/jrzg/2009-12/26/content_1497435.htm; in Chinese: http://www.pkulaw.cn/fulltext_form.aspx?Db=chl&Gid=125300
[100] Zhai, X., Ng, V., & Lie, R. (2016). (Same reference as in footnote 97).
[101] NPC (2010). The Tort Liability Law of the People's Republic of China. http://www.gov.cn/jrzg/2009-12/26/content_1497435.htm

Section 3: Regulatory measures that govern technologies that achieve the same or similar results as germ line genome editing

64 In this section we will summarize legal and regulatory measures that govern existing or prospective technologies that achieve the same or similar results as human germ line genome editing. The following technologies will be discussed: (1) Pre-implantation Genetic Diagnosis (PGD), (2) Prenatal genetic screening (PGS) and Prenatal Genetic Testing (PGT), (3) Somatic Gene Therapy, as well as (4) Stem Cell Therapy.

3.1. The regulatory framework for Pre-implantation Genetic Diagnosis (PGD)

65 PGD is a procedure in which in-vitro created embryos are tested for chromosomal or genetic abnormalities, prior to being used in an IVF cycle. PGD is in many cases an alternative to human germ line genome editing because it allows identifying embryos that are free from specific genetic conditions.[102] PGD has been practiced in China since 1999 (source). In the context of its population control policies the Chinese government has attached great importance to the prevention of transmitting genetic disorders, and it has encouraged PGD and other forms of prenatal genetic screening (PGS) and prenatal genetic testing (PGT).[103]

66 PGD services are regulated as part of China's Regulation on Reproductive Technologies (2003).[104] Licensed IVF clinics are entitled to provide PGD to patients, but require a staff member with relevant training. Institutions must also offer other prenatal diagnostic services and provide in-house genetic counseling service (MOH 2003).

3.2. The regulatory framework for prenatal genetic screening (PGS) and Prenatal Genetic Testing (PGT)

67 Prenatal genetic screening (PGS) and prenatal genetic testing (PGT) are aspects of prenatal care that aim to detect genetic abnormalities in embryos or fetuses, typically in the early stages of gestation. It forms an alternative to human germ line gene editing, because it allows for the selective abortion of affected embryos or, in some cases, for the introduction of preventive measures that may delay the onset of a disease.

68 While routine pregnancy check-ups are covered in China by national health insurance, these do currently not include prenatal genetic testing. Pregnant mothers have to pay for prenatal genetic testing from their own pocket.[105] There is no government-funded prenatal genetic screening program in China, and

[102] Ishii, T. (2017). Reproductive medicine involving genome editing: clinical uncertainties and embryological needs. *Reproductive BioMedicine Online*, *34*(1), 27-31.
[103] Zhuang, G. L., & Zhang, D. (2003). Preimplantation genetic diagnosis. *International Journal of Gynecology & Obstetrics*, *82*(3), 419-423.
[104] Qiao, J., & Feng, H. L. (2014). Assisted reproductive technology in China: compliance and non-compliance. *Translational pediatrics*, *3*(2), 91.
[105] Zhang, D., Ng, V. H., Wang, Z., Zhai, X., & Lie, R. K. (2015). Eugenics and Mandatory Informed Prenatal Genetic Testing: A Unique Perspective from China. *Developing world bioethics*.

prenatal genetic testing is a voluntary but increasingly accessible prenatal service available especially in urban areas.[106]

69 Prenatal genetic testing services are regulated through the 'Administrative Measures for Prenatal Diagnosis Technology' (产前诊断技术管理办法), which are ministerial guidelines issued by the MOH in 2003.[107] The guidelines specify the qualifications of institutions offering prenatal genetic diagnosis, relevant procedures such as informed consent, issues related to genetic counseling, and the responsibilities and qualifications of medical staff.[108]

70 Article 17 of the administrative measures states that physicians shall give advice on Prenatal testing, in one of the following cases: (i) too much or too little amniotic fluid; (ii) the abnormal development of a foetus or the malformation of a foetus; (iii) exposure to substances which may lead to the abnormal foetal development in early pregnancy; (iv) a family history of an inherited diseases or having given birth to an abnormal foetus previously; (v) over 35 years of age. As specified in Article 24, in case of the discovery of abnormal foetal development physicians shall give advice on whether to continue or terminate pregnancy.[109] As Zhang and colleagues point out in their analysis of the regulation, advice on abortion is given if a fetus is suffering from a genetic disease of a serious nature, if the fetus has another serious defect, and also if continuation of gestation may endanger the life of a pregnant woman, or seriously impair her health.[110]

3.3. The regulation for Non-Invasive Prenatal Genetic Testing (NIPT)

71 The regulation for NIPT underwent various twists and turns in China. From 2011 to 2014 NIPT was offered to pregnant women in a legal grey area. The technology was not licensed by the CFDA, but the number of companies who were offering NIPT grew rapidly. Then, in February 2014, the China Food and Drug Administration (CFDA) and the National Health and Family Planning Commission (NHFPC) issued a notification that announced that all NIPT services in hospitals had to stop immediately, until after a phase of regulatory deliberation and until a formal approval mechanism for NIPT services was in place. During a period of four months the CFDA implemented a new licensing procedure and by the end of June the first two detection kits for NIPT were approved for market use. In July 2015, the NHFPC announced the 'Notification of NHFPC on the cancellation of Class III of medical technology clinical applications access approval' (国家卫生计生委关于取消第三类医疗技术临床应用准入审批有关工作的通知).[111] In this notification the NHFPC changed the regulatory rules for the registration of medical devices and diagnostic tools. NIPT

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[106] Zhang, D., Ng, V. H., Wang, Z., Zhai, X., & Lie, R. K. (2015). (Same reference as in previous footnote).
[107] http://www.moh.gov.cn/mohzcfgs/s3577/200804/17612.shtml
[108] Sui, S., & Sleeboom-Faulkner, M. (2007). Commercial genetic testing in mainland China: Social, financial and ethical issues. *Journal of Bioethical Inquiry*, *4*(3), 229-237.
Zhang, D., Ng, V. H., Wang, Z., Zhai, X., & Lie, R. K. (2015). Eugenics and Mandatory Informed Prenatal Genetic Testing: A Unique Perspective from China. *Developing world bioethics*.
[109] http://www.moh.gov.cn/mohzcfgs/s3577/200804/17612.shtml
[110] Zhang, D., Ng, V. H., Wang, Z., Zhai, X., & Lie, R. K. (2015). Eugenics and Mandatory Informed Prenatal Genetic Testing: A Unique Perspective from China. *Developing world bioethics*.
[111]http://www.nhfpc.gov.cn/yzygj/s3585/201507/c529dd6bb8084e09883ae417256b3c49.shtml

technology was now still required to register with the CFDA, but exempt from further clinical testing. NIPT is now widely and legally available to pregnant women in China.[112]

3.4. The regulatory framework for gene therapy and somatic gene editing

72 Gene therapy includes the insertion of genes into cells with the purpose to treat or prevent diseases. Older experimental approaches to gene therapy include (i) the genetic replacement of mutated genes that cause disease, the (ii) inactivation or "knocking out" of mutated genes, or (iii) the introduction of new genes into the body that help to fight a disease.[113]

73 With the advent of CRISPR/Cas-9 genome editing technologies a new paradigm for gene therapy has emerged, in which 'the sequence of the human genome can be precisely manipulated to achieve a therapeutic effect. This includes the correction of mutations that cause disease, […] or the removal of deleterious genes or genome sequences'.[114] Several medical disorders that could be prevented by human germ line genome editing, can potentially be cured through gene therapy and somatic genome editing. In contrast to human germ line genome somatic genetic modifications affect only the individual patient, but they are not inherited by offspring.[115] China was the first country in the world that has approved the commercial use of a gene therapy in 2003. In contrast to the USA and the European Union where gene therapy clinical trials were blocked before 2012, clinical research in this field has flourished in China since almost 20 years now.[116] Chinese researchers have also been the first who have applied somatic gene editing in human patients, in a lung cancer trial that started in 2016.[117]

74 Because China's regulatory framework for gene therapy would most likely also play a role for reproductive forms of genome editing (at least if China's ban on heritable germ line gene editing would be lifted in the future), we have discussed details of this regulation already in Section 2.4.4 above.

3.5. The regulatory framework for clinical stem cell research and applications

75 The development of stem cell-based treatments is another therapeutic strategy that may in some cases achieve similar results as germ line genome editing. Stem cell therapies make use of the regenerative potential of stem cells to cure diseases. While stem cell medicine is still at an early stage, it is widely assumed

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[112] This section is based on the following article: Zeng, X., Zannoni, L., Löwy, I., & Camporesi, S. (2016). Localizing NIPT: Practices and meanings of non-invasive prenatal testing in China, Italy, Brazil and the UK. *Ethics, Medicine and Public Health*, *2*(3), 392-401.
[113] NIH 2017. Gene Therapy. https://ghr.nlm.nih.gov/primer/therapy/genetherapy
[114] Maeder, M. L., & Gersbach, C. A. (2016). Genome-editing technologies for gene and cell therapy. *Molecular Therapy*.
[115] National Academies of Science (2017). Human Genome Editing: Science, Ethics and Governance. Available at: https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance
[116] Li, H., Lei, J., Xu, F., Yan, C., Guimerans, M., Xing, H., ... & Zhang, D. (2017). A study of sociocultural factors on depression in Chinese infertile women from Hunan Province. *Journal of Psychosomatic Obstetrics & Gynecology*, *38*(1), 12-20.
[117] Cyranoski, D. (2016). CRISPR gene-editing tested in a person for the first time. *Nature News*, *539*(7630), 479.

that stem cell-based treatments have the potential to treat various currently incurable diseases.

76 Researchers, hospitals and small-to-mid size corporations have been active in clinical stem cell research for many years. Aside to more systematic clinical studies China has made headlines with the emerging of a large grey-area market of experimental stem cell interventions that have been offered to patients on a for-profit basis, but in the absence of reliable evidence on the safety and efficacy of these treatments.

77 In recent years China's health regulators have increasingly sought to control these grey area applications. Stem cell clinical research and applications is presently regulated through two regulatory instruments: (1) the 'Administrative Measures for Clinical Stem Cell Research (Trial)' (干细胞临床研究管理办法，试行), [118] and the 'Stem Cell Preparations Quality Control and Pre-clinical Research Guidelines (Trial)' (干细胞制剂质量控制及临床前研究指导原则， 试行), which were both joint-issued by the NHFPC and the CFDA in 2015.[119]

78 These regulatory documents state that stem cell-based interventions have to be evaluated through methodical clinical studies and follow from systematic preclinical evidence. These trials must comply with the CFDA's 'Drug Clinical Trial Quality Specifications' and can only be conducted in level 3 hospitals – which is the highest ranked hospital category in China. They also stipulate the standards and technical procedures for the collection, manufacturing and storage of stem cells in the context of clinical use and summon that hospitals are required to establish stem cell preparation facilities that are compliant with international GMP standards.[120]

79 Noteworthy is also, that the 2015 regulation has prohibited to advertise unproven stem cell treatment and charging patients for taking part in experimental interventions or clinical studies. Despite this prohibition, though, the provision of non-systematically proven and unauthorized stem cell treatments has continued, albeit on a smaller scale.[121]

[118] http://www.nhfpc.gov.cn/qjjys/s3581/201508/28635ef99c5743e294f45e8b29c72309.shtml
[119] http://www.sda.gov.cn/WS01//CL1355/127241.html
[120] Rosemann, A., & Sleeboom-Faulkner, M. (2016). New regulation for clinical stem cell research in China: expected impact and challenges for implementation.
[121] Rosemann, A., Bortz, G., Vasen, F., & Sleeboom-Faulkner, M. (2016). Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations. *Regenerative Medicine*, *11*(7), 647-657.

Section 4: Insights into current public and political debates in China

80 In this section we present insights into public debates on human germ line genome editing in China. For this purpose we have searched for information on websites and in journal articles. Experts, primarily researchers and bioethicists, shape most of these debates, including people with close links to policy making. Our impression was that a more comprehensive public and media debate that would include viewpoints from a more diverse set of stakeholders has not yet happened in China. We also did not find results from of public deliberation projects, neither from government-related bodies nor from civil societal organizations.

81 A shortcoming of this section is, however, that we have not yet focused on discussions in the diverse landscape of Chinese microblogs. As has been widely reported, the microblogsphere in China has evolved to a platform for zealous debate, collective deliberation and the voicing of critical opinions, especially among younger people.[122]

82 1. The largest proportion of comments on websites and journals that we came across supported human germ line genome editing but called for careful ethical and regulatory scrutiny.

Professor Xinqing Zhang, who is also an author of this background paper, has cautioned that due to the lessons learned from the early development of gene therapy clinical trials and embryonic stem cell research, hyperbole and scientific misuse of human embryo and germ line gene editing should be avoided from the beginning. China and other countries ought to establish a comprehensive regulatory framework to meet the technical and ethical demands specific to such clinical trials.[123]

Prof Jianqiao Liu, from the Third Affiliated Hospital of Guangzhou Medical University (who is also co-author of the first publication that reports gene editing in healthy embryos[124]) states that: 'Some of the ethicists believe that human genes are innate and that one should not change them: Human genes cannot be changed, how can you dare to change them? But our perceptions of ethics are constantly progressing and changing. 40 years ago, unmarried cohabitation could be a cause for imprisonment. Now, if men and women fall in love, it is rare if a couple does not live together before marriage for some time. Ethics is constantly changing. […] Technology in itself is neutral, but the crucial point is how to use it. If technology, through management measures, regulation and a corresponding infrastructure can be controlled and standardized, mankind can experience proper benefits'.[125]

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[122] Tong, Y., & Lei, S. (2013). War of position and microblogging in China. *Journal of Contemporary China*, *22*(80), 292-311.
[123] Zhang, X.Q. (2016) Risk-Benefit Analysis of CRISPR-Cas germline editing clinical research on human embryos and its ethical governance, Science & Society (Chinese) 6: 12-21.
[124] Tang, L., Zeng, Y., Du, H., Gong, M., Peng, J., Zhang, B., ... & Liu, J. (2017). CRISPR/Cas9-mediated gene editing in human zygotes using Cas9 protein. *Molecular Genetics and Genomics*, 1-9.
[125] Tang, in: Li, X. (2017) Dialogue: A scientist who genetically modified human embryos. The paper, March 21, 2017. Available at: http://www.thepaper.cn/newsDetail_forward_1643724

An anonymous author that was cited in an article in the Chinese Journal of Science commented: 'The development of technology itself is very fast, but the Chinese gene editing research is in a relatively disorderly state. With regard to both, its scientific organization and the corresponding ethical management. Laws and regulations are relatively weak, and need to be strengthened. There are a lot of regulatory gaps in gene editing in our country. In order to encourage innovation and to avoid ethical risk and social disputes, we need to clarify which studies should be supported and which should be strictly prohibited'.[126]

82 2. Some people accepted the importance of basic research, but they oppose the clinical use of human embryo gene editing:

The geneticist Professor Hongqi Wang, for example, has suggested that Chinese researchers should not conduct basic research of gene editing in human germ cells and embryos at will, and especially not proceed with clinical research since this research field is in an extremely immature phase.[127]

The bioethicist and policy maker Professor Renzong Qiu has argued that at present the application of gene editing in human germ lines should be discouraged and that research that aims for human enhancement should be ruled out.[128] However, Qiu also recognizes that in the long run human germ line genome editing may be conducive to the prevention of human genetic disease and to the benefit of children from genetically predisposed families.[129] At the same time, Qiu Renzong points out that human embryo gene modification research also faces many ethical issues. For this reason, scientists cannot arbitrarily conduct research. According to Qiu this research field requires more ethical considerations and the development of adequate ethical norms.[130]

83 3. Still others thought that human germ line research will be difficult to stop:

Chen Guoqiang, a professor of biology at the School of Life Sciences at Tsinghua University states: 'If this technology is used in people in the future, the first mature [genetically modified] individual will be a much-desired breakthrough. While this step may probably bring about some problematic effects and repercussions, every technology undergoes a period from premature to mature. Currently, many heritable diseases do not have well-developed treatments. This [embryo gene editing] is a possibility of exploration. But [at present] used embryos should not be allowed to grow beyond the embryonic stage. Scientific

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[126] Anonymous, in: Gan, X. (2016). Chinese gene editing research develops fast: Ethics and regulatory issues are not resolved. Chinese Journal of Science. July 14, 2016. http://3g.163.com/touch/article.html?docid=BRUDKJ1100097U81&qd=pc_adaptation (in Chinese)
[127] Wang HQ (2016) Ethical inquiries about CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. Protein and Cell 6: 363-72
[128] Qiu RZ (2016) Research and application of gene editing technologies: an ethical perspective. Medicine and Philosophy (in Chinese) 37: 1-7.
[129] Wang, D., Tan, J., and D.H. Fu (2015) The transformation of human embryonic genes leads to ethical controversy. Jiangkang Bao (Health Newspaper). May 5, 2015. http://www.jkb.com.cn/news/depth/2015/0505/368192.html (in Chinese).
[130] Wang, D., Tan, J., and D.H. Fu (2015) (Same reference as in previous footnote).

research is always risky. If it is forbidden, for fear of risks, then it is difficult for science to progress'.[131]

Professor Zhao Shimin, a biologist at Fudan University in Shanghai, stated that the advent of human germ line gene editing is inevitable: 'This technology has already been used on plants and animals. The next will be human beings'. But he also cautioned that there are limitations and risks: 'Changing the sequence of genes can lead to unexpected problems that could spread from generation to generation and cause other defects or illnesses. […] While such studies should be allowed, they must be strictly controlled in the laboratory. […] A large number of uncontrolled editing of DNA can potentially lead to human extinction'.[132]

84 4. Others pointed to the potential dangers of this research field:

Professor Jianyuan Luo from the Peking University Health Science Centre said that: 'Although in animal experiments, these imperfections will not cause serious consequences, in human applications the relevant genetic changes will be inherited from generation to generation. This may lead to new diseases or even unpredictable consequences. This is dangerous'.[133]

Chengzhi Wang, an associate researcher of the Chinese Academy of Science has commented on the Internet: 'Mankind never gives up the realization of their dreams. This can be seen with the increasing popularity of plastic surgery hospitals. Imagine that human embryonic genes could be edited without restrictions. Then, a variety of genetic diseases will be completely eradicated. But humans will not be satisfied with this, because humans also want to get "better genes." […] But if the Pandora box has been opened, the consequences may be unpredictable. We should not forget that there are always some crazy people in mankind. When they have mastered some resources, they follow the path of human nature'.[134]

[131] Chen, in: China Broadcasting Network (2015) Chinese scientists have successfully modified human embryonic genes to trigger ethical controversy. April 27, 2015. http://money.163.com/15/0427/08/AO6OHH2I00254TI5.html (in Chinese)
[132] Zhao, in: Xinhua Net (2015) Genetically Modified "Designer" baby: Chinese scientists provoke controversy. April 24, 2015. http://legal.people.com.cn/n/2015/0424/c188502-26899038-3.html (in Chinese)
[133] Luo, in: Wang, D., Tan, J., and D.H. Fu (2015) The transformation of human embryonic genes leads to ethical controversy. Jiangkang Bao (Health Newspaper). May 5, 2015. http://www.jkb.com.cn/news/depth/2015/0505/368192.html (in Chinese).
[134] Wang, in: Wang, D., Tan, J., and D.H. Fu (2015) The transformation of human embryonic genes leads to ethical controversy. Jiangkang Bao (Health Newspaper). May 5, 2015. http://www.jkb.com.cn/news/depth/2015/0505/368192.html (in Chinese).

Section 5: A discussion of the cultural, social and political values and ambitions that underpin public and policy debates on human gene editing in China

85 In this section we explore some of the wider cultural, social and political and also economic values and ambitions that are likely to influence public and policy debates on heritable forms of human genome editing in China. We would like to point out, however, that the social and cultural situation in China is complex, diverse and in a state of continuous transition. While several of the factors we introduce are likely to influence debates on human genome editing in China, systematic empirical research into the cultural, social, political and economic values, attitudes and aspirations that shape these debates is urgently needed.

5.1. Cultural Conceptions of Infertility

86 In the patriarchal and patrilineal tradition of Chinese society conceptions of fertility and the family in China, have stressed the obligation for sons to carry on the family line for centuries.[135] This attitude is influential also in the present.[136] Infertility and childlessness are, at least in more rural contexts, still widely regarded as a form of personal failure and are often paralleled by feelings of shame, depression and stigma.[137] Considering this situation, basic and preclinical forms of gamete and embryo gene editing research, that address the causes of infertility, problems of embryo development during IVF, and other factors that prevent the development of a healthy child, can be expected to receive general support among the Chinese public.

5.2 Cultural Conceptions of Disability

87 Despite widespread efforts to raise awareness for people with disability during the last two decades, discrimination and stigma of disability is still prevalent in China, also with regard to the birth of a disabled child. As Zhang and colleagues have pointed out, for families in poor areas, the birth of a child with genetic defects does greatly affect their quality of life:

> ‘There is relatively little support and protection from the local government for people born with genetic defects. Children with genetic defects would likely be subjected to discrimination from family and members of the community. In many cases, parents would resort to abandoning or even killing their child after birth with genetic defects. For these families with low income and quality of life to begin with, having a child with genetic defects is an unbearable burden’.[138]

[135] Greenhalgh, S., & Winckler, E. A. (2005). *Governing China's population: from Leninist to neoliberal biopolitics*. Stanford University Press.
[136] Li, B., Gao, N., Zhang, Z., Chen, Q. M., Li, L. J., & Li, Y. (2017). Historical and Clinical Experiences of Gene Therapy for Solid Cancers in China. *Genes*, *8*(3), 85.
[137] Li, B., Gao, N., Zhang, Z., Chen, Q. M., Li, L. J., & Li, Y. (2017). (Same reference as in previous footnote). ; Fu, B., Qin, N., Cheng, L., Tang, G., Cao, Y., Yan, C., ... & Lei, J. (2015). Development and validation of an Infertility Stigma Scale for Chinese women. *Journal of psychosomatic research*, *79*(1), 69-75.
[138] Zhang, D., Ng, V. H., Wang, Z., Zhai, X., & Lie, R. K. (2015). Eugenics and Mandatory Informed Prenatal Genetic Testing: A Unique Perspective from China. *Developing world bioethics*.

88 But there are also possible cultural reasons for the stigma surrounding disability. As pointed out by the historian Frank Dikoetter, according to cultural assumptions embedded in folk beliefs, Confucian ideas of the family and rural traditions:

'A person is seen as the culmination of his or her ancestors and is held responsible for the health of future generations. By this logic, a pregnant woman's behavior and attitude directly influence the wellbeing of her baby, and a deformed or retarded child reflects a moral failing on the part of the parents'.[139]

89 While the dismissing of such "feudal" thoughts has been a key element of China's socialist modernization, these kind of rural beliefs are still likely to have an effect in the presence. Parents of disabled children have reported frequent discriminatory behaviors by others,[140] and public schools have regularly refused children with disabilities.[141] According to the sociologist Maya Wang, among the 'estimated 83 million people with disabilities in China [in 2013], more than 40 per cent were illiterate and at least 15 million lived on less than US$1 a day, underscoring the lifelong consequences of a lack of access to education'.[142]

5.3. The One-Child Policy and the need for a healthy child

90 The pressure for a healthy child has increased under the 35 years of the country's One-child policy (which since January 2016 has been transformed to a Two-child policy). As family members remain an important source of economic support among the elderly, especially in rural areas, the birth of a healthy, strong and capable child is a pre-requisite for wellbeing and survival.[143] An important component of the One-child policy has been the promotion of "fewer but higher quality births". The wish for a healthy, "high quality" child that fulfills parental ambitions of upward mobility and filial support during old age, has become an important cultural value in Chinese society.[144] The cultivation of "high quality" children is sought to be achieved through improvement of education, child health programs, nutritional awareness, extra-curricular learning and other activities.[145] This has put increasing pressure on both, children and parents.[146]

91 Various commentators have speculated that due to the high level of competition and social pressure in Chinese society, which is partly the result of the One-child policy, attitudes toward human enhancement are likely to be more favorable in

[139] Dikoetter, F. (1998) Imperfect Conceptions: Medical Knowledge, Birth Defects, and Eugenics in China. New York, New York: Columbia University Press
[140] McCabe, H. (2007) Parent Advocacy in the Face of Adversity: Autism and Families in the People's Republic of China. *Focus on Autism and Other Developmental Disabilities*. **22** (1): 39–50.
[141] Wang, M. (2013) Chinese children with disabilities denied access to education. *South China Morning Post*. 17 September, 2013. http://www.scmp.com/print/comment/insight-opinion/article/1310977/chinese-children-disabilities-denied-access-education
[142] Wang, M. (2013) (Same reference as in previous footnote).
[143] Zhang, Y., & Goza, F. W. (2006). Who will care for the elderly in China?: A review of the problems caused by China's one-child policy and their potential solutions. *Journal of Aging Studies*, *20*(2), 151-164.
[144] Greenhalgh, S., & Winckler, E. A. (2005). *Governing China's population: from Leninist to neoliberal biopolitics*. Stanford University Press.
[145] Greenhalgh, S. (2010). *Cultivating Global Citizens* (Vol. 12). Harvard University Press.
[146] Zhang, Y., & Goza, F. W. (2006). Who will care for the elderly in China?: A review of the problems caused by China's one-child policy and their potential solutions. *Journal of Aging Studies*, *20*(2), 151-164.

China, compared to other countries, and that this may increase support for non-medical forms of human genome editing as well as other enhancement technologies.[147]

5.4. Less frequent use of public engagement

92 Another factor that is likely to influence public debates on human germ line gene editing is that forms of citizen deliberation and public engagement with science and technology issues is less common in China, than for instance in the UK, other EU countries and the USA. While calls for more inclusive forms of decision-making and actual forms of public consultation exist also in China,[148] there is a less-well established tradition of public engagement and the extent, the methodologies and procedures that are used for public deliberation, and the publics and stakeholders that are consulted vary.[149] People are typically not used to debate fundamental technology developments – before they take place and impact society, and policy decisions are primarily discussed among experts.[150] Public viewpoints are currently clearly under-represented in public debates on human germ line gene editing in China, and more detailed knowledge of the actual perceptions, concerns and possibly hopes among citizens would be helpful.

Scientific Illiteracy as an obstacle to Public Engagement

93 A factor that contributes to the less frequent use of citizen participation and public engagement is also a relatively low scientific literacy rate among "ordinary" people (laobaixing) in China (as in most other countries). Considering that human genome editing is a very specific research area, it is difficult for people (even for highly-educated people and experts from other disciplines) to fully understand the characteristics, uncertainties, limitations, risks and forms of dual use of emerging biotechnologies. This poses an important barrier to public engagement.

94 One reason of the relatively low level of scientific literacy is that public opinions on human genome editing are often polarized. It is by many either assessed as "excellent" or as "very bad", but in both cases often based on poor judgment and insufficient knowledge. Popular media like 'China Science Newsletter' (中国科学报) and the 'China Social Sciences Today' (中国社会科学报) pay more attention to the ethical and regulatory issues of gene editing, and provide a platform for

[147] Schaefer, O. (2016). China will develop the first genetically enhanced 'superhumans', experts predict. Daily Mail. August 3, 2017. http://www.dailymail.co.uk/sciencetech/article-3721991/China-develop-genetically-enhanced-superhumans-experts-predict.html

[148] Zhai, X., Ng, V., & Lie, R. (2016). No ethical divide between China and the West in human embryo research. *Developing world bioethics*.

[149] Abelson, J., Forest, P. G., Eyles, J., Smith, P., Martin, E., & Gauvin, F. P. (2003). Deliberations about deliberative methods: issues in the design and evaluation of public participation processes. *Social science & medicine*, *57*(2), 239-251.;
Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf

[150] He, B. (2011). Civic engagement through participatory budgeting in China: Three different logics at work. *Public Administration and Development*, *31*(2), 122-133.

interested lay persons to know more. The articles published here are also often picked up and published by other websites. But overall, the role of the media could be stronger in promoting more inclusive forms of public understanding of gene editing.

5.5. Uncritical acceptance of S&T agendas?

95 Another aspect that is likely to affect debates and policy decisions on human germ line gene editing is the existence of a social and political climate in China that emphasizes rapid economic growth. The forceful promotion of science and technology research has become a key strategy for economic and social development in China and is seen as a means to successfully compete in the global economy. The economic achievements of the last decades and the ascent of China to a leading science nation have strongly legitimized the aggressive promotion of techno-science. But these achievements have also sometimes led to the uncritical support for scientific and technological agendas, without fully examining their consequences or potential societal implications. Even though (as we have shown in Section IV above) involvement of experts in public debates is common, a critical engagement with science and technology issues from the side of civil society and the public seems often lacking. Such voices, however, could contribute important insights into otherwise closed processes of expert decision-making.

Section 6: Implementation

96 Implementation is a key issue when discussing China's legal and regulatory system for ARTs and human embryo, gamete and germ line gene editing research. While state authorities have issued a growing number of regulatory instruments and laws to govern technology developments in the life and health sciences, consistent implementation has often proved difficult.

6.1. Challenges to implementation in China

97 A first reason is that China's large territory and huge population make it extremely difficult to control what is going in the thousands of research institutes, hospitals and corporations that are involved in biomedical and biotechnology research and applications. A second reason is that the regulatory oversight of health care and health science research, including preclinical research, is dispersed across a wide range of government departments and agencies. This can raise conflicts of interests and problems of coordination.[151] A third reason is that, as mentioned in Section 1.1.2 national level regulations serve often only as general guidance and that the development of implementation strategies is left to government departments at a provincial-level. This can result in significant variation of the interpretation and the implementation of regulatory standards.[152] A forth challenge is that military and police universities, research institutes and hospitals have their own regulatory bodies and rules that are often different from the regulatory system for civil institutions. As pointed out in Section 1.1.3 military and policy hospitals enjoy typically a greater level of experimental freedom, which enables for-profit practices that in state hospitals would be prohibited.[153] A fifth factor is that many scientists and also regulators consider the adoption and implementation of more stringent regulatory norms as an obstacle for biotech innovation, because they are seen to prevent local research and economic opportunities (especially those opportunities that thrive on a certain level of regulatory and administrative flexibility).[154]

98 For these reasons, the implementation system in China is less consistent than in the UK, and there is also a greater level of variation between different provinces and regions.[155] The UK governs more through statutory authorities which have been set up by law, and which implement legislation in connection with clearly defined sanctions. In China, on the other hand, ministerial guidelines are the most widely used regulatory instrument for biotech and biomedical innovation. However, ministerial guidelines have typically 'less "authority" and carry less sanctions than rules promulgated by the State Council […] or laws passed by the

[151] Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf
[152] Sui, S., & Sleeboom-Faulkner, M. (2015). Commercial genetic testing and its governance in Chinese society. *Minerva*, *53*(3), 215-234.; Zhang, J. Y. (2012). *The cosmopolitanization of science: stem cell governance in China*. Palgrave Macmillan.
[153] Sui, S., & Sleeboom-Faulkner, M. (2015). (Same reference as in previous footnote).
[154] Sleeboom-Faulkner, M., Chekar, C. K., Faulkner, A., Heitmeyer, C., Marouda, M., Rosemann, A., ... & Patra, P. K. (2016). Comparing national home-keeping and the regulation of translational stem cell applications: an international perspective. *Social Science & Medicine*, *153*, 240-249.
[155] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303

National People's Congress'.[156] Nevertheless, Chinese laws such as the 'Drug Clinical Trial Regulations Law on Practicing Doctors', the 'Tort Liability Law of the PRC' and also regulations (issued by the state Council) such as the 'Regulation on the Governance of Medical Institutions' are powerful legal instruments that allow to shut down medical institutions, to withdraw licenses, and to persecute medical practitioners in case of malpractice.

6.2. Gap between regulatory rules and actual practices

99 Problems with implementation and sometimes also the toleration of grey area practices have in various technology fields led to considerable gaps between regulation and actual practice.[157] As mentioned in Section 2.3, China's regulatory framework for ART does specifically prohibit surrogacy, and yet a large grey area market for surrogacy services has emerged in China in recent years.[158] Even though China's health authorities have closed down several hundreds of ART clinics in the mid-2000s (for offering un-authorized IVF services), many clinics and ART companies have been lured by a growing demand for surrogacy services, and accept the risk of punishment.[159] In response to these informal services, the Chinese government is now seeking to make surrogacy legal.[160]

6.3. The implementation of regulatory instruments for human embryo, gamete and germ line gene editing

100 The current regulatory framework for basic and preclinical research that involves embryo or germ cell gene editing is relatively well developed. By adhering to the 14-day rule, requiring ethical review and informed consent for embryo and germ cell donation and by prohibiting the transfer of research embryos to a woman, China's current regulation does – at least in terms of its basic rules – not much differ from other countries.

101 A difference with the UK is, that embryo research in the UK is generally reviewed by the HFEA. The HFEA is a national-level statutory agency that grants licenses for research projects if the requirements of the Human Fertilization and Embryology Act (the UK's ART law) have been met. In China, on the other hand, ethical review is de-centralized and lies solely in the hand of involved institutions: the IVF clinic in which the embryos or germ cells are procured and the

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[156] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303

[157] Sleeboom-Faulkner, M. E. (2016). The large grey area between 'bona fide'and 'rogue'stem cell interventions—Ethical acceptability and the need to include local variability. *Technological Forecasting and Social Change*, *109*, 76-86.

[158] Yan, A. (2017). Official Ban is No Brake on China's Surrogacy Sector. South China Morning Post (February 17, 2017). Available at: http://www.scmp.com/news/china/society/article/2071548/official-ban-no-brake-chinas-surrogacy-sector; Su, Y.Y. (2017). Public Opinion on Legalizing Surrogacy in China?. Impact Ethics. Available at: https://impactethics.ca/2017/03/15/public-opinion-on-legalizing-surrogacy-in-china/

[159] Doering, O. and A. Wahlberg (2007). Bionet First Workshop Report: Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards. Available at: http://bionet-china.org/wp-content/uploads/2013/10/BIONET_1st_Workshop_Report.pdf

[160] Yan, A. (2017). (Same reference as in footnote 158).

departments or research institute in which the research is conducted. Sometimes these can also be the same institutions.

102 A problem is, of course, that the exclusive reliance on institutional review boards (IRBs) or ethics committees can easily result in a collision of interests.[161] A related problem is that there is limited oversight of IRBs through external bodies and also that separate conflict-of-interest committees in universities and hospitals are rare.[162] Moreover, in the absence of standardized norms for the review and approval of (basic and preclinical forms of) human germ cell or embryo genome editing research, the scientific, ethical and also moral criteria that are used to review and approve such research are likely to differ between institutions. In theory at least this could result in the approval of research that in other research institutions in China would not be approved and that would be seen as ethically problematic.

103 However, as mentioned in Section 2.4.1 above, with the issuing of the 'Measures for the Ethical Review of Biomedical Research Involving Humans' external oversight of local IRBs and ethics committees (by higher-level government bodies) is sought to be strengthened. New mechanisms to improve and review the work of local IRBs have been introduced. In which ways these new oversight mechanisms will work and are implemented in practice remains to be seen.

6.4. The transition toward potential clinical applications

104 As described in Section 2 above, the genetic modification of human gametes, zygotes and embryos for reproductive purposes is currently banned in China. However, as mentioned in Section 2.4, the lifting of this ban in the future is not unlikely. If this would happen additional regulatory instruments that address the specific characteristics and risks of heritable forms of human genome editing would be necessary. It is at present not clear whether the resources, administrative infrastructure and the political will could be mobilized in order to consistently enforce a regulatory framework for clinical research and applications in this field. Presently, however, we have not heard of any attempts to lift the ban or to revise China's regulation for human germ cell or embryo gene editing research, let alone to develop new regulation for clinical research.

105 Nevertheless, considering the fact that numerous clinics in China have offered premature, illegal and sometimes highly risky forms of clinical interventions in other research areas – gives some cause for concern. In light of this situation, the provision of premature and potentially risky forms of heritable genome editing in China cannot be precluded. It is true, however, that first-in-human applications that involve heritable genome editing of gametes or zygotes will be a radical step forward. So radical in fact that it is likely to spark off a huge wave of media attention and lead to widespread calls for consistent regulatory intervention. This would most likely force regulators in China (and most other countries) to rapidly

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[161] Morin, K., Rakatansky, H., Riddick Jr, F. A., Morse, L. J., O'Bannon III, J. M., Goldrich, M. S., ... & Spillman, M. A. (2002). Managing conflicts of interest in the conduct of clinical trials. *JAMA*, *287*(1), 78-84; Levinsky, N. G. (2002). Nonfinancial conflicts of interest in research. *The New England journal of medicine*, *347*(10), 759.

[162] Warrell, D. et al. (2009). Cure Committee Report: China–UK Research Ethics. UK Medical Research Council. Available at: http://www.mrc.ac.uk/Utillities/Documentrecord/index.htm?d=MRC006303

intervene and to crack down and prevent potential forms of “premature”, “rogue” or “illegal” clinical applications.

Concluding Remarks

106 We are not aware that Chinese regulators are currently planning the issuing of additional regulatory instruments for human gamete, embryo or germ line genome editing. There are also no indications that the ban on the reproductive use of genetically modified germ cells, zygotes or embryos shall be lifted any time soon. However, this does not mean that considerations for regulatory adjustments are not already underway. Among the scientists, bioethicists and other experts that publicly comment on human genome editing in China, the majority argue in favor of this technology field, but within a robust regulatory frameworks that prevents misuse, exaggerated expectations and the possible exploitation of patients. Implementation is probably the greatest challenges that could hamper developments in human genome editing in this field, and that could cause harm to the reputation of China as a science location and possibly the field of human germ cell and embryo research as a whole.

107 Regarding a potential shift towards clinical research and reproductive applications various questions arise. A first question concerns reactions of the Chinese media and public. How would citizens and the increasingly privatized media in China react to the availability of heritable genome editing? And how would the public and the media react to non-systematically proven and “premature” clinical applications? Insights from public responses and media coverage on grey area stem cell therapies in China have shown that, there was a gradual transition from initial fascination and praise, to a more critical public awareness, which gradually forced regulators to intervene and to prohibit irresponsible forms of for-profit clinical interventions.[163]

108 A second question concerns regional variation in China. As in other technology fields one can expect significant regional differences of the ways in which regulation and policies is interpreted and implemented. While some regions are likely to enforce regulatory rules for human genome editing strictly, others are likely to be more permissive. What consequences will this have? Will permissive implementation of regulatory rules in certain regions accelerate and enable first-in-human applications, and possibly even pave the way to non-medical applications and genetic enhancement, as some commentators have claimed?

109 A third question concerns the role of army hospitals and the military. Will military hospitals and research institutes embrace the idea of heritable genome editing? And will the Health Department of the Army General Logistics Department devise a different (more permissive) regulatory approach for this research field compared to civil institutions, as happened with clinical stem cell research and many other fields of medicine research?

[163] Rosemann, A. (2013). Medical innovation and national experimental pluralism: Insights from clinical stem cell research and applications in China. *BioSocieties*, *8*(1), 58-74.

110 At a more general level, if a shift toward first-in-human applications takes place in China (which we think it will, at a certain moment of time), much will depend on whether this level of heterogeneity can be managed. If not, regional variation, divergent interpretations of rules and regulatory exceptions in military or private hospitals are likely to prevent homogenous implementation. Consistent implementation hinges on the political prioritization to prevent premature or irresponsible forms of clinical applications, and also whether there will be sufficient resources to implement reliable control structures, so as to enforce national regulation across the extensive geographical, social and cultural space of contemporary and future China.

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